REMARKS/ARGUMENTS

In response to the Office Action of August 28, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

In order to provide the Examiner with an opportunity to fully consider all of the issues, a Request for Continuing Examination is filed concurrently herewith.

Claim Status/Support for Amendments

Claims 22-26 are under examination. Claims 22 and 26 have been amended. Claims 1-21 were cancelled in a previous Response (filed on September 18, 2002). Claims 22-26 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

The method of claim 22 consists of specific steps. Claim 22 has been amended to clearly indicate these specific steps. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 22 is limited to these specific steps. Step (c) was amended to provide antecedent basis for the term "autoantibody". Claim 22 was also amended to indicate that the comparison level is statistically significant. Support for this comparison level is found throughout the

specification as originally filed; for example at page 23, lines 7-9 (and Figure 2); page 23, lines 19-21 (and Figure 7); and page 32, line 22 to page 33, line 16. Claim 22 was also amended to indicate the high diagnostic values which can be achieved by the claimed method; sensitivity of about 77%, specificity of about 95% and a likelihood ratio (LR) value of about 14.8. Support for this amendment can be found in the instant specification as originally filed at page 26, lines 10-13; page 46, line 21 to page 48, line 12 and Figures 8 and 9.

Claim 26 was amended to indicate that the claim is dependent upon claim 25 and not on claim 22.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form has cited the references they have not been considered.

Applicants note that an Information Disclosure Statement was filed in the instant application on November 14, 2001 and further a copy of the PTO-1449 form was attached to the Office Action

mailed on March 3, 2002 indicating that the Examiner had considered the references cited therein.

The references cited within the specification, but not included in the Information Disclosure Statement filed on November 14, 2001, provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Rejection under 35 USC 112, second paragraph

Claims 22-26, as presented on June 3, 2003, stand rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 22 is vague and indefinite because it is unclear when the heparin is added to the ELISA (i.e. is heparin added before the sample or to the sample or is heparin added before the addition of a label or after the addition of a label?).

Applicants respectfully disagree with the Examiner's assertion.

The disclosure clearly indicates that heparin is added to the sample of body fluid prior to performing the assay; support is found throughout the specification as originally filed; for example at page 21, lines 11-16; page 37, lines 12-17; and page 41,line 21

to page 42, line 12.

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 103(a)

Claims 22-26, as presented on June 3, 2003, stand rejected under 35 USC 103(a) because the claimed invention is allegedly unpatentable over Bloch et al. (US 6,183,988) in view of Voumvourakis et al. (Greek Microbiology Organization Newsletter 37:666-672 1992) and further in view of Pesce et al. (Journal of Immunological Methods 87:21-27 1986).

Applicants respectfully disagree with the Examiner's determination that the claimed subject matter is obvious.

In order for an Examiner to establish a *prima facie* case of obviousness, three basic criteria must be met (MPEP 2142). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations.

Multiple sclerosis(MS) is an immunological disease characterized by a long latent period followed by a pattern of acute attacks and remissions (see the instant specification at page 2, line 22 to page 3, line 2). Until the instant invention there was no useful method for MS patients to monitor their disease status.

The instant invention teaches a method for diagnosing or monitoring multiple sclerosis (MS)by measuring levels of anti-myelin basic protein (MBP) antibodies in bodily fluid samples having a high diagnostic value as evidenced by a sensitivity of about 77%; a specificity of about 95% and a likelihood ratio (LR) of about 14.8.

The Examiner cites three references (Bloch, Voumvourakis and Pesce) which allegedly support the determination of the obviousness of the instant invention. Each of the references is deemed to disclose an element(s) of the claimed method. The Examiner apparently believes that disclosure of the elements is equivalent to motivation to combine elements.

It has been established that the mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (see MPEP 2143.01).

The situation in *In re Mills* is similar to the instant situation. The invention of Mills is directed to an apparatus for

producing aerated cementitious material. The reference relied upon was a patent issued to Mathis. All of Mills' apparatus structure is present in the machine described by Mathis, however, the court decided that Mathis did not render the invention (of Mills) obvious because Mathis does not suggest Mills' claimed apparatus *(In re Mills* 16 USPQ2d 1430).

Applicants respectfully submit that, although the references (Bloch et al, Voumvourakis et al. and Pesce et al.) relied upon by the Examiner contain elements of Applicants' method, there is no suggestion to combine the information in the references to arrive at the claimed invention, and thus the claimed method is rendered non-obvious.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time that the invention was made to substitute myelin basic protein as taught by Voumvourakis et al. for the protein in Bloch et al. because Voumvourakis et al. shows that multiple sclerosis has been associated with the presence of antibodies against myelin basic protein.

Bloch et al. teach a method for detecting autoimmune disease in a mammal by assaying the anti-Sp140 antibody levels in a biological sample obtained from the mammal.

Voumvourakis et al. teach a method for the detection of anti-MBP (myelin basic protein) in the serum of patients with MS.

While it is possible to combine the teachings of these references, the Examiner is respectfully reminded that the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination (see MPEP 2143.01).

The Examiner contends that one of ordinary skill in the art would be motivated to use anti-MBP antibodies in the method disclosed by Bloch et al; however, the Examiner does not show and/or explain why one would be so motivated. Bloch et al. teach an assay for detection of a variety of autoimmune diseases and do not specifically discuss detection of MS. Furthermore, Bloch et al. do not discuss any antibody other than the anti-Sp140 antibody nor does Bloch et al. suggest assaying levels of multiple autoantibodies for any autoimmune condition. How would one of ordinary skill in the art select which antibody, anti-Sp140 antibody or anti-MBP antibody, is better for diagnosing and/or monitoring MS? Without an answer to this question, one of ordinary skill in the art would not be able to ascertain any advantages of modifying the teachings and therefore, would not have any reason to substitute anti-MBP for anti-Sp140 when carrying out the assay disclosed by Bloch et al.

The Examiner further asserts that it would have been obvious to one of ordinary skill in the art to determine anti-MBP IgG and IgM as taught by Voumvourakis et al. for the method of Bloch et al.

because Voumvourakis et al. teach that the pathogenesis of multiple sclerosis involves antibodies directed against myelin basic protein and the aim of the study was to investigate anti-MBP in the serum of patients with multiple sclerosis since the occurrence of these antibodies in subjects with multiple sclerosis is controversial.

While it is possible to combine the teachings of these references, the Examiner is respectfully reminded that the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination (see MPEP 2143.01).

The Examiner contends that one of ordinary skill in the art would be motivated to use anti-MBP IgG and anti-MBP IgM antibodies in the method disclosed by Bloch et al; however, the Examiner does not show and/or explain why one would be so motivated. Bloch et al. do not discuss any advantages for use of a particular isotype. In their statistical analysis, regarding levels of IgG, IgM and IgA isotypes, Voumvourakis et al. disclose that only the patients with the IgG and IgA isotypes showed a difference in antibody levels which was statistically significant from levels shown in control patients. Thus, Voumvourakis et al. actually teaches away from the use of the IgM isotype. How would one of ordinary skill in the art know which isotype gives the most accurate diagnosis and/or monitoring of MS? Why would one of ordinary skill in the art choose to use an IgM isotype when, according to the study of Voumvourakis

et al. , patients did not show a difference in the level of antibody that was statistically significant from the level of antibody shown in the control patients? Without answers to these questions, one of ordinary skill in the art would not be able to ascertain any advantages of modifying the teachings and therefore, would not have any reason to be motivated to make any alterations in antibody isotype when carrying out the assay disclosed by Bloch et al.

The Examiner also asserts that it would have been obvious to one of ordinary skill in the art to incorporate the use of heparin as taught by Pesce et al. into the modified method of Bloch et al. because Pesce et al. show that non-specific reactivity of the cationic protein can almost be completely eliminated by carrying out the antibody-antigen incubation in the presence of heparin and further discloses that the use of heparin allows for the enhancement of antigen-antibody reactions because of neutralization of the positive charges of the antigen.

While it is possible to combine the teachings of these references, the Examiner is respectfully reminded that the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination (see MPEP 2143.01).

The Examiner contends that one of ordinary skill in the art would be motivated to incorporate the use of heparin as taught by Pesce et al. in the method disclosed by Bloch et al; however, the Examiner does not show and/or explain why one would be so motivated. Bloch et al. do not discuss whether the nature of their disclosed protein, Sp140, is cationic or anionic nor do Bloch et al. mention any problems with their assay resulting from non-specific reactivity due to charge interactions. Thus, one of ordinary skill in the art would not recognize a need for any charge-neutralizing agents such as heparin when carrying out the methods of Bloch et al. and therefore would not be motivated to make any additions of heparin or other such compounds when carrying out the assays.

Furthermore, the instant invention teaches a method for diagnosing or monitoring multiple sclerosis (MS)by measuring levels of anti-myelin basic protein (MBP) antibodies in bodily fluid samples having a high diagnostic value as evidenced by a sensitivity of about 77%; a specificity of about 95% and a likelihood ratio (LR) of about 14.8. None of the three references which allegedly support the determination of the obviousness of the instant invention disclose any information regarding the diagnostic value of their assays. How would one of ordinary skill in the art know which combination of elements to select to achieve the desired result, for example, to achieve an assay with a diagnostic value

equivalent to or better than the diagnostic value of the claimed assay? Without an answer to this question, one of ordinary skill in the art would need to attempt multiple assays before arriving at the desired result.

It was established by the decision in *In re Geiger* (2 USPQ2d 1276) that obviousness cannot be established by combining teachings of prior art to produce claimed invention, absent some teaching, suggestion, or incentive supporting combination, and thus, although it might have been obvious to one skilled in the art to try various combinations of teachings of three prior art references to achieve the claimed method (method of Geiger), such evidence does not establish a *prima facie* case of obviousness. The application of Geiger is directed to a method for inhibiting scale formation on and corrosion of metallic parts in cooling water systems by use of compositions containing (1) a sulfonated styrene/maleic anhydride (SSMA) copolymer, (2) a water soluble zinc compound, and (3) an organo-phosphorous acid compound or water soluble salt thereof. The Examiner used three references, each disclosing some element of the composition of Geiger, to reject the claims under 35 USC 103(a). The court decided that there was no teaching, suggestion or incentive to support the combination and indicated that one of skill in the art might find it "obvious to try" various combinations of known scale and corrosion prevention agents; however, the establishment of "obvious to try" does not meet the

standard for obviousness under 35 USC 103(a).

Applicants respectfully submit that the situation in the instant application is analogous to the situation in the application of Geiger and assert that the Examiner has only established a case for "obvious to try" rather than establishing obviousness of the claimed invention.

The Examiner apparently believes that disclosure of the elements is equivalent to motivation to combine elements. Although all of the elements of Applicants' method may be found in various references in the prior art, there is no suggestion and/or motivation in the references themselves or in the prior art to combine these elements. Accordingly, one of ordinary skill in the art having access to all three references would not be able to arrive at the method of the instant inventors without prior knowledge of the data of the instant inventors and would thus have to attempt numerous trial assays before arriving at a successful result. Therefore, Applicants respectfully submit that the Examiner is applying an improper "obvious to try" rationale in support of the obvious rejection (see MPEP 2145 X B and *In re O'Farrell* 7 USPQ2d 1673).

The Examiner must also show that one of ordinary skill in the art would have a reasonable expectation of success when modifying the references or combining reference teachings.

The Examiner does not address the issue of whether one would

have a reasonable expectation of success when modifying the references or combining reference teachings.

Multiple sclerosis(MS) is an immunological disease characterized by a long latent period followed by a pattern of acute attacks and remissions (see the instant specification at page 2, line 22 to page 3, line 2). Rapid, reliable diagnostic measures and earlier treatment are of paramount importance for prediction and possible prevention of relapse.

At the time of the instant invention there was a need for a useful method for MS patients to monitor their disease status. The claimed method offers an assay which achieves a high level of diagnostic value which satisfies the need in the art.

The instant inventors evaluated the diagnostic performance of their assay and found that their assay exhibits high sensitivity (77%) and specificity (95%). See the specification at page 47, lines 10-13 and Figure 9.

The likelihood ratio (LR) permits a calculation of the probability of a disease for a specific test result and specific disease prevalence. Likelihood ratios with a value greater than 10 are usually judged to be of high diagnostic value. The assay of the instant invention offers an LR of 14.8 and thus is proven to be a reliable diagnostic tool for MS. See the specification at page 48, lines 7-12 and Figure 9.

Neither the cited references nor the general knowledge in the

art suggests to one of ordinary skill in the art which elements to select to obtain an assay with a diagnostic value and likelihood ratio equal to or better than the diagnostic value and likelihood ratio of the instant invention. Thus, one of ordinary skill in the art would have no reasonable expectation of achieving such a level of diagnostic performance when modifying element selection in the assay since one of ordinary skill in the art would not know the proper combination to insure superior diagnostic capabilities and likelihood ratios.

Furthermore, assays for assessing the level of anti-MBP antibodies in MS patients have produced contradictory results, i.e. some assays found low levels of anti-MBP antibodies (see attached abstract of Panitch et al. Archives of Neurology 37(4):206-209 1980; reference 1 and attached abstract of Chou et al. Neurology 33:24-28 1983; reference 2) and some assays found high levels of anti-MBP antibodies (see attached abstract of Garcia-Merino et al. Journal of Neurology, Neurosurgery and Psychiatry 49(9):1066-1070 1986; reference 3). Considering the known uncertainties of assay results, one of ordinary skill in the art would have little reason to expect reliable diagnostic performance of such assays.

The Examiner must also show that the prior art reference or references when combined teach or suggest all of the claim limitations.

It was established above that the prior art references (Bloch

et al, Voumvourakis et al. and Pesce et al.) do not teach or suggest all of the limitations of claims 22-26, i.e. a method of diagnosing and/or monitoring MS having a high clinical diagnostic value as shown by a sensitivity of about 77%, a specificity of about 95% and an LR value of about 14.8.

Thus, Applicants respectfully submit that the Examiner has failed to satisfy all the criteria necessary to establish a proper rejection of claims under 35 USC 103(a); 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine teachings; 2) reasonable expectation of success and 3) the references when combined must teach or suggest all of the claim limitations.

In light of all of the above remarks, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and further contend that a clinician of ordinary skill in the art, having the references (Bloch et al., Voumvourakis et al. and Pesce et al.) in front of him/her would not have the information and motivation necessary to arrive at Applicants' invention.

Thus, it is respectfully submitted that the combination of Bloch et al., Voumvourakis et al., Pesce et al. and information known in the prior art fails to reasonably teach or suggest to one of ordinary skill in medicine/biology the elements of Applicants'

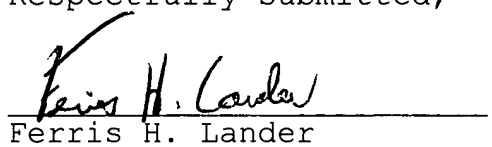
method as specifically set forth in claims 22-26 as presented herein.

Accordingly, Applicants respectfully submit that the claimed method distinguishes over the prior art and respectfully request that this rejection of claims 22-26 under 35 USC 103(a) now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)
\\Ns2\server\CLIENT FILES\2100-2199\2132 -Syn-X\2132_000024 - MS Diagnostic\Amendments\2132_024_2ndRC:

2132.024 Examiner copy reference 1

1: Arch Neurol. 1980 Apr;37(4):206-9.

CSF antibody to myelin basic protein. Measurement in patients with multiple sclerosis and subacute sclerosing panencephalitis.

Panitch HS, Hooper CJ, Johnson KP.

A solid phase radioimmunoassay was used to detect antibodies to myelin basic protein (MBP) in the CSF of patients with multiple sclerosis (MS) and subacute sclerosing panencephalitis (SSPE). F(ab')2 fragments prepared from SSPE IgG retained their activity, which showed that the assay measures a true antigen-antibody reaction rather than nonspecific adherence to IgG to MBP. Samples of CSF from 48 patients with MS and 30 patients with SSPE were tested and, in both conditions, antibody activity was significantly greater than in controls, when tested at identical IgG concentrations. In MS, levels of antibody were highest in patients with acute exacerbations and lower in patients in remission, which supported the hypothesis that autoimmunity to a myelin antigen may play a role in the pathogenesis of the disease. The reaction with MBP was consistently more pronounced in SSPE than in MS. In view of the association of SSPE with measles virus and the presence of high titers of measles antibody in the CSF, antibodies to measles and to MBP may be directed against similar antigenic determinants.

PMID: 6153890 [PubMed - indexed for MEDLINE]

2132.024 Examiner copy reference 2

Limits: **Publication Date from 1983 to 1983**

1: Neurology. 1983 Jan;33(1):24-8. Related Articles, Links

Failure to detect antibodies to myelin basic protein or peptic fragments of myelin basic protein in CSF of patients with MS.

Chou CH, Tourtellotte WW, Kibler RF.

Using the sodium sulfate precipitation radioimmunoassay and solid-phase radioimmunoassay, we measured antibody to intact human myelin basic protein and myelin basic protein peptic fragments, residues 1-44, 45-89, and 90-170, in CSF. Comparable levels of binding were obtained for MS and normal CSF by both tests. The increased amount of CSF IgG in MS patients cannot be attributed to specific antibody against myelin basic protein or its peptic fragments.

PMID: 6184646 [PubMed - indexed for MEDLINE]

Limits: **Publication Date from 1986 to 1986**

2132.024
Examiner copy
reference 3

1: J Neurol Neurosurg Psychiatry. 1986 Sep;49(9):1066-70. Related Articles, Links

Serum and cerebrospinal fluid antibodies against myelin basic protein and their IgG subclass distribution in multiple sclerosis.

Garcia-Merino A, Persson MA, Ernerudh J, Diaz-Gil JJ, Olsson T.

IgG class antibodies reactive with myelin basic protein (MBP) were determined by enzyme-linked immunosorbent assay (ELISA) in serum and cerebrospinal fluid (CSF) of 37 patients with multiple sclerosis and a control group of 32 patients with tension headache or psychoneurosis. Using standardised amounts of IgG from CSF and serum in ELISA, significantly higher mean antibody levels were found in CSF as well as in serum from the patients with multiple sclerosis. Ten (27%) of the multiple sclerosis CSF samples and 15 (41%) of the multiple sclerosis sera revealed anti MBP antibody levels exceeding 2 SD of the control group. Seven patients (19%) showed exclusive or higher levels of anti MBP antibodies in CSF, suggesting synthesis within the central nervous system. Analysis by ELISA for IgG subclasses of anti MBP antibodies revealed that they were restricted to IgG 1 in four patients and IgG 3 in one.

PMID: 2428940 [PubMed - indexed for MEDLINE]